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Review Article

Caries Vaccine: The Journey So Far

Krishnendu Chatterjee*

Orthodontics and Dentofacial Orthopedics, Private Practitioner and Consultant Orthodontist, Kolkata, India

***Corresponding Author:** Dr. Krishnendu Chatterjee, Orthodontics and Dentofacial Orthopedics, Private Practitioner and Consultant Orthodontist, Kolkata, India.

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Abstract

Dental caries is one of the most common diseases affecting human beings. Despite the various preventive and restorative treatment procedures that have been put to use in clinical dentistry, the epidemic of dental caries has still continued to remain at a global level. The last few decades have seen remarkable progress in the development of agents to combat the arch criminal of dental caries- *Streptococcus mutans*, in the form of caries vaccine. The main focus of it is targeted towards either eliminating the caries pathogens or by suppressing the virulence of the same. Although, more clinical trials are needed to evaluate the safety and practical feasibility of the application of these agents as potential caries vaccines, the journey of caries vaccine has come a long way.

Keywords: Dental Caries; Caries Vaccine; *Streptococcus Mutans*; Recent Advances

Introduction

Dental caries remains one of the most pervasive infectious diseases of mankind, despite the availability of various preventive measures. It is a major oral health concern in most industrialized countries, affecting 60-90% of school going children and adults with the maximum prevalence in several Asian and Latin-American countries [1]. The WHO estimates have reported an incidence of tooth decay in over 5 billion people [2].

The multi-factorial pathophysiology behind dental caries constitutes a complex time dependent interaction between acid-producing bacteria, like *Streptococcus mutans, Lactobacillus acidophilus, Lactobacillus fermentum, Actinomyces viscosus,* and fermentable carbohydrate substrate, along with many host factors including the biological and mechanical structure of teeth and constitution, quantity and quality of the saliva. Dental caries affects both the crowns and root portion of teeth, in all age groups in all population. *S. mutans* has been researched as the most prevalent and chief causative microorganism species among others implicated in dental caries [3].

Today, the armamentarium of the dentist is laden with various preventive and restorative strategies against caries, like pits and fissure sealants, minimally invasive dentistry, SMART restorative materials [4]. But these are all expensive procedures and have not been able to reach wide range of population crossing the economic barriers. Fluoride therapy is difficult to administer due to lack of single community water supply and associated risk of overdose. Chemotherapeutic agents like chlorhexidine cause staining of teeth [2].

The success associated with eradication of diseases like chicken pox and poliomyelitis by vaccination has paved the path towards working to obtain a similar vaccine for the global epidemic of dental caries, which can be well suited for public health applications, especially in environments that do not lend themselves to regular health care [3]. The focus of the present review is on the research and contributions done so far and the recent developments in a vaccine to prevent dental caries.

Caries vaccine and its mode of action

Scientists thought that the prevention of formation of dental caries can be done by the development of antibody against dental caries, known as caries vaccine. Caries vaccine is a vaccine currently under development to treat dental caries by inoculating against bacteria commonly known to contribute to their formation, particularly *S. mutans* [42].

Thirty years ago, British and American scientists demonstrated that experimental protection could be achieved by immunization with mutans streptococci (reviewed by Michalek and Childers) immunologically intercepting properties of these organisms that led to disease.

There are several phases in the molecular pathogenesis of *S. mutans* and each of these phases offer targets for immunological intervention. The first step involves the colonizing the oral cavity by acidogenic streptococci. This is established by binding of antigen I/II in *S. mutans* with the mucin-like glycoproteins found in parotid and sub-mandibular saliva, that constitute the host-derived components in the dental pellicle covering the tooth surfaces [4].

Antibodies could intervene this process by either blocking the receptors necessary for colonization (e.g., adhesins) or accumulation (e.g., glucan-binding domains of GBPs and GTF) within the dental biofilm. The antimicrobial activity of salivary antibody may be synergistically enhanced or reprogrammed with mucins or lactoferrin which form the innate components of immunity. Adhesins, Glucosyltransferase (GTF), Glucan-Binding Protein (GBP), Dextranases are some of the specific antigenic components researched extensively as target of vaccine [3].

Another approach towards the development of caries vaccine is through external passive supplementation of the antibodies. The major benefit derived from this method is the avoidance of any risks that might arise from active immunization, but conversely, due to its passive nature there is no immunological memory that is induced thereby resulting into a short life of the administered antibodies in the mouth which is only a few hours at most or up to 3 days in plaque. Several approaches for passive antibody administration have also been tried for effects on indigenous *S. mutans* [6,7].

Advances in modalities

DNA Vaccine [1-3]

Chinese scientists from the Wuhan Institute of Virology have discovered a new fusion anti-caries DNA vaccine which has been able to deliver positive outcomes in the prevention of dental caries. It has been observed that cell surface protein PAc and glucosyltransferases (GTFs) are the two significant virulence factors in *S. mutans*. Further it has been found that the glucosyltransferases have two functional domains which are an N-terminal catalytic sucrose-binding domain (CAT) and a C-terminal glucan-binding domain (GLU). Studies in gnotobiotic animals revealed that the cell surface protein PAc and the GTF domain C-terminal glucan-binding domain (GLU) were successful in reducing *S. mutans* induced dental caries. On the contrary, it was found that there is a weaker protective effect against *S. sobrinus*.

Delivery Systems and Adjuvants [2-5]

There is a paucity of clinical trials to demonstrate the efficacy of active immunization with antigen based dental caries. Topical application of soluble peptide antigens on oral mucosa has seldom resulted in long term IgA responses. This has led to the research efforts to be redirected to develop immunomodulators or adjuvants and delivery systems that augment mucosal responses to the caries vaccine. Studies conducted on humans by Russell, Childers, Smith., *et al.* have used GTF derived from *S. sorbinus*, which demonstrated increased IgA antibody levels. Adjuvants like aluminium phosphate, and enteric coating were employed to enhance the action of the GTF in these various studies. In order to outweigh the aforementioned shortcomings, various new approaches are being worked on.

Synthetic peptides [1-3,5]

Animal or human derived antigens have the potential for hypersensitivity reaction, which can be avoided by the use of chemically synthesized peptides that can enhance the immune response. In humans, the antibodies generated by the synthetic peptides were both anti-peptide and anti-native and activation of IgG was associated with T-cell proliferative responses.

Research on synthetic peptide approaches has demonstrated immunogenicity of alanine-rich repeat region of Ag I/II from *S. mutans*. The protective immunity offered by mucosal immunization

using peptides derived from the alanine-rich region showed higher levels of IgG antibody than that derived from proline-rich region. The induced antibodies circulate both in the gingival crevicular fluid and also the saliva.

Coupling with Cholera and *E. coli* toxin subunits [1,4,5]

Nontoxic unit of the Cholera Toxin (CT) being a powerful mucosal immunoadjuvant, can be used to couple with proteins in order to disrupt *S. mutans* colonization and induce mucosal immunity to various bacterial and viral pathogens in animals. IgA responses to mucosal administration of peptides or soluble proteins alone are generally not elevated or sustained, hence enhanced mucosal response is observed when small amounts of CT or *E. coli* heat labile enterotoxins (LT) are added. This enhancement of mucosal immune response encompasses intragastrically or intranasally applied *S. mutans* antigens or associated peptides as well.

Recombinant vaccines [1,2,5]

Recombinant technology, applied in the development of synthetic peptides targeted to make caries vaccine, allow expression of larger functional sequences. The potent and effective vectors utilized for recombinant technique fusion are avirulent Salmonella strains. Studies on rats have reported effective oral immunization against *S. sorbinus* with recombinant Salmonella, without the persistent requirement of recombinant *S. typhimurium* in the Peyer's patches or spleens to induce immunity.

Liposomes [1,2,4,5].

Liposomes are vesicles enclosed within bilayered phospholipid membrane and have been used in anti-cancer research to specifically target anomalous cells and allow effective drug delivery. It has been hypothesized that liposomes facilitate M cell uptake and delivery of antigens to lymphoid elements of inductive tissue which results in enhanced mucosal immune response to streptococcal carbohydrate and GTF.

Liposomes have shown immune response to double in rat models and increase IgA antibodies in humans.

Microcapsules and microparticles [1-3,6]

In order to attain enhanced mucosal immune response, combinations of antigen with various types of particles have been attempted. Poly (lactide-co-glycolide) (PLGA) offers the advantages of controlled and sustained rate of release without eliciting any inflammatory response to the polymer and has hence been used as local delivery system. Oral immunization with microspheres allow the vaccine to be released effectively and in a controlled fashion in the gut associated lymphoid tissues (GALT), which induce mucosal IgA anti-toxin antibody response.

Conjugate vaccines [1,2,5]

Chemical conjugation of functionally associated protein/peptide components with bacterial polysaccharides can lead to interception of more than one aspect of molecular pathogenesis in S. mutans. A markedly enhanced immunogenic response is noted to the T-cell-independent polysaccharide component by conjugation of protein with the polysaccharide.

ISCOM [2,4,5]

These are solid particles combined with antigens along with biocompatible detergent and adjuvant carriers, which can be useful in prevention of dental caries. Protein antigens of caries vaccine can be incorporated with them. Besides these liposomes, biogradable microspheres and bioadhesives can be used as carrier for the antigens.

Plantigens and Plantibodies [8-11]

Newer technology has developed production of antigen-antibody action against cariogenic microbes from plants. According to investigators it gives better action against dental caries, without causing side effects.

In 2008, Caro^{RX}, an advanced plantibody (plant- derived antibody) which is produced in tobacco plants and is secretory IgA in nature, was seen to prevent dental caries [12].

Transgenic plants

One of the recent steps in utilization of passive immunization against dental caries is by the generation of antibodies in transgenic plants such as *Nicotiana tabacum*. The four components of the vaccine are generated in different transgenic *Nicotiana tabacum* plants, which are - a murine monoclonal antibody kappa chain, a hybrid immunoglobulin A-G heavy chain, a murine joining chain, and a rabbit secretory component. The vaccine, which is colourless

and tasteless, can be painted onto the teeth rather than injected and is the first plant derived vaccine from genetically modified (GM) plants [7-11].

The advantages of this are, easily exchangeability of genetic material, possibility of manipulation of the antibody structure to maintain the specificity of the antibody while the constant region can be modified to adapt to human conditions, thus avoiding cross reactivity, and possibility of easier and inexpensive large scale production thereby allowing treatment for large population [2-4,7].

Apples and Strawberries [1,5].

Research has been carried out in order to develop a peptide that can be injected into fruits to block caries causing *S. mutans*. Scientists at the Guys Hospital, London have already isolated a gene and the peptide and are trying to find ways to deliver the peptide into the mouth through apples and strawberries.

Prof. David James (2000) observed that apples and strawberries can be used in development of caries vaccine by injecting peptides which block *S. mutans* into the fruits which would be delivered in the mouth to reduce dental caries.

Tobacco [8-11].

Recently, studies by the likes of Nagarajappa and Pavia., *et al.* have indicated lower incidence of dental caries and lower oral microbial pathogen including *Streptococci* count in tobacco users. Although there is evidence of literature contradictory to this, stating chewing tobacco leads to attrition and extrinsic stains that offer a protective effect against dental caries, rather than an actual inhibition to the patho-physiology of dental caries formation.

Bovine milk and whey [1,2]

Polyclonal IgG antibodies introduced in bovine milk and whey, by immunizing the cattle with vaccine containing *S. mutans*, help in reduction of the caries level. Whey, also used in the form of mouth rinse, resulted in a lower bacterial count of *S. mutans* in plaque.

Egg-yolk [1-3]

In 1990, hens' egg-yolk IgY antibodies was introduced by Hamada. Vaccines used were formalin killed whole cells and cell associated GTFs helped in caries reduction.

Recent Advances

The most recent advance in the arena of caries vaccine has been by the use of a protein p1025. This protein mimics the surface coating of S. mutans. This has a significant action by triggering false stimuli on S. mutans, which suggests the unavailability of vacant sites for attack on the tooth [13-15].

Conclusion

It is an understatement to mention that more research is needed in the days to come to proceed towards achieving an agent which can, not just be used as a potent caries vaccine, but also be available to the general population at less expense. This review work is an attempt to bring under one umbrella all the research that has been done in the development of caries vaccine, in order to provide necessary information that can help researchers to carry forward the work. A big shortcoming to this research work is the problem with proper financial and infrastructural support, as the project is targeted towards elimination and eradication of dental caries which is the bread and butter for major portion of the dental health care and profession.

Yet dentists are eagerly looking forward to tiring efforts and contributions made by engineers and scientists in further advancement and development of caries vaccine into reality, which shall be a blessing in treatment of medically or physically challenged patients, as well as in geriatric and pediatric dentistry.

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